THE PREVALENCE OF *LEGIONELLA* AND MYCOPLASMA SEROPOSITIVITY IN THE ELDERLY IN CAPE TOWN

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B. ABSTRACT

Background

Community acquired pneumonia causes 5,9% of deaths in elderly South Africans. Mortality rates are increased in those in whom initiation of therapy with an appropriate agent has been delayed. Whereas *Mycoplasma pneumoniae* and *Legionella pneumophila* are sensitive to the macrolides or tetracycline, they do not respond to the currently recommended first-line agents for community acquired pneumonia, penicillin or a cephalosporin. It was therefore necessary to assess the prevalence of exposure to these 2 organisms in the elderly in order to determine whether a modification in the recommendations may be justified.

Methods

Study population and survey

Subjects were residents of 4 old age homes in Cape Town who were older than 60 years and willing to participate. Written consent was obtained, a demographic and medical history questionnaire was completed, and a sample of blood was drawn.

Laboratory methods

The indirect fluorescent antibody tests (Zeus Scientific Inc., New Jersey, USA) were used to detect the presence of antibodies to *Mycoplasma pneumoniae* and *Legionella pneumophila*.

Results

The participation rate in this study was high, with 88,4% (677/766) taking part. Seropositivity for both of these organisms was low. There were 17 participants (2,51%) with antibodies to mycoplasma (IgG only in 8, IgM only in 1, and both IgG and IgM in the remaining 8). Titres were low with only 1 IgM titre of 16 , and only 3 IgG titres of 64. Antibodies to *Legionella* were demonstrated in only 9 participants (1,33%). All these titres were 128 or above.

Conclusions

It is concluded that first-line therapy for community acquired pneumonia should adhere to the current guidelines published by the South African Pulmonology Society. There is no indication for the routine use of agents active against *Legionella* or mycoplasma. Clearly, these antibiotics should be introduced if specific pointers to infection with one of these organisms are found.

Because of the low seropositivity rate, the indirect fluorescent antibody test for these 2 agents has a high specificity in this population. This may be of use in making a diagnosis in an acute infection.

Further studies are required to elucidate the immunological response to these organisms in elderly persons. A further survey should be done to determine the seropositivity rate to these agents in community dwelling elderly.

C. INTRODUCTION

1. COMMUNITY ACQUIRED PNEUMONIA IN THE ELDERLY

In the United States community acquired pneumonia is the fourth most common cause of death in the elderly (Ebright & Rytel, 1980), while in South Africa 5,9% of all deaths in people over the age of 65 are due to pneumonia (Bradshaw et al., 1987). The older patient with pneumonia is more likely to have a severe illness with a complicated course and to require hospitalisation (Fein et al., 1991; Marrie et al., 1985). Mortality rates in community acquired pneumonia in adults vary from 12 to 15%, but are approximately doubled in the elderly (Venkatesan et al., 1990; Marrie et al., 1985) (Tables 1 and 2). Pre-existing co-morbid illnesses such as chronic obstructive lung disease, congestive heart failure, and diabetes mellitus, as well as a less efficient immune system (Sen et al., 1995) contribute to this increase in morbidity and mortality. (Note that the term "elderly" is usually used to refer to adults aged 65 years and older, but that some authors regard age 60 or older as "elderly".)

An aetiologic agent is identified in about 70% of community acquired pneumonias in adults, but in only 45% in the elderly (Marrie et al., 1985). The reported prevalence rates of different aetiological agents vary from one study to another (Table 1), from country to country (British Thoracic Society, 1987; Blanquer et al., 1991; Fang et al., 1990; Karalus et al., 1991; Lim et al., 1989), within a country (Macfarlane et al., 1982; White et al., 1981), and from one time to another within the same geographical area (Macfarlane et al., 1982; Woodhead and Macfarlane, 1987). *Streptococcus pneumoniae* is the most common cause in most studies conducted in adults and elderly populations accounting for 13 to 76% of cases, with

Haemophilus influenzae being the second most common cause responsible for some 8 to 28% (Tables 1 & 2). A high prevalence of Gram-negative infections has been noted in elderly subjects with pneumonia, *Staphylococcus aureus* being prominent in this group as well (Garb et al., 1978; Ebright & Rytel, 1980; Verghese and Berk, 1983). Mixed infections with more than one organism are more common in the elderly (Fein et al., 1991).

Garb et al. (1978) compared community acquired pneumonia in the elderly with nursing home acquired pneumonia and found that Gram-negative infections were much more common in the latter group, 40% having *Klebsiella pneumoniae* as compared with 9% in those living in the community. *Staphylococcus aureus* was almost twice as common in the nursing home patients (26%) as in the community dwelling subjects (14%). In their study *Streptococcus pneumoniae* occurred in only 26% of nursing home residents with pneumonia as compared with 43% in the community acquired group, while *Haemophilus influenzae* was relatively uncommon in the former (6%) as compared with the latter (20%). The high mortality rate (40%) in nursing home patients as compared with those from the community (20%) was ascribed to the differences in aetiology.

Mycobacterium tuberculosis has been shown to be a particular problem among the elderly in old age homes in South Africa (Morris & Nell, 1988). It may present as an acute pneumonia (Prout et al., 1983), and so infection with this organism must be considered in cases of community acquired pneumonia in older persons, especially if resident in old age homes.

The variation in prevalence rates of adult pneumonia due to *Legionella* or mycoplasma is quite marked with mycoplasma being responsible for 1 to 18% of adult pneumonias, while

Legionella has been demonstrated in 2 to 15% (British Thoracic Society, 1987; Maartens et al., 1994; Macfarlane et al., 1982; Marrie et al., 1985). The role of these two organisms in the aetiology of community acquired pneumonia in the elderly will be discussed in some detail later.

2. CLINICAL MANIFESTATIONS OF PNEUMONIA IN THE ELDERLY

It is well recognised that pneumonia may have an atypical presentation in older patients. This may be a major factor leading to a delay in diagnosis, thus contributing to the increased morbidity and mortality that has been noted in these patients.

Typical symptoms of pneumonia are less frequently elicited in patients who are of advanced age or have chronic illness, and may be completely absent in about 10% (Harper & Newton, 1989). The presence of cognitive impairment contributes to this by making an accurate history more difficult to obtain. Alteration in mental status may be a presenting feature, and may be due to the development of an acute confusional state or a deterioration in cognitive function as compared with baseline status as a result of the infection. Acute confusion was present in the majority (65%) who died in the study by Starczewski et al. (1988). The development of weakness, a decline in physical function, falls, or gastro-intestinal symptoms may alert the physician to the possibility of pneumonia (Harper & Newton, 1989).

There may be no fever at the time of presentation. Marrie et al. (1985) in 138 patients with community acquired pneumonia showed that 57% of those over the age of 65 were apyrexial at presentation as compared with 27% under 65. Likewise, cough is not necessarily a prominent feature in the elderly patient with pneumonia, and may be absent in approximately a third (Harper & Newton, 1989).

An elevation of the respiratory rate is a subtle sign of pneumonia which may precede other clinical findings by some 3 to 4 days (McFadden et al., 1982). A tachycardia greater than 100

is present at some time in about 60% with pneumonia, and is the presenting feature in 15% (Harper & Newton, 1989). Leucocytosis is absent in about a third. However, Harper and Newton (1989) noted that, even in those patients who have no symptoms to suggest a diagnosis of pneumonia, some abnormality suggesting infection, such as an elevated temperature or white cell count, was usually present.

The typical signs of segmental or lobar consolidation of the pneumonic lung, such as dullness to percussion or bronchial breathing, are infrequently elicited in older patients (Berk et al., 1982). In approximately 25% with documented pneumonia, the breath sounds are entirely normal, while clinical signs in areas of radiographic abnormality are detected in only a quarter (Osmer & Cole, 1966). To add to the diagnostic confusion is the fact that crackles may be present in elderly persons who do not have pneumonia or cardiac failure. This may be due to closure of lower zone airways which occurs during normal resting ventilation (Holland et al., 1968).

The rate of radiographic resolution decreases with increasing age. In the British Thoracic Society study (1987) of community acquired pneumonia, the chest radiograph had returned to normal in 50% of those aged 33 to 53 years by 4,5 weeks, while 9 weeks were required for a similar improvement in those aged 65 to 74 years.

3. ATYPICAL PNEUMONIA

The term "atypical pneumonia" was first used by Reimann in 1938 to describe a group of patients with clinical pneumonia which was unlike the pneumonia caused by the usual bacterial pathogens or by the influenza virus (Reimann, 1938). No causative agent for this syndrome could be identified at that time. Cold agglutinins were discovered in the sera of some of these patients in 1943, and, in 1961, Channock was able to show that this syndrome was due to the agent which later became known as *Mycoplasma pneumoniae* (Channock et al., 1961). Subsequently the term "atypical pneumonia" has come to include pneumonias due to *Chlamydia psittaci*, the *Legionella* species, and *Coxiella burnetii*, as well as the more recently identified organism, *Chlamydia pneumoniae*.

Yung et al. (1987) feel that the term "atypical pneumonia" should not be used as a collective term for pneumonia caused by these organisms, nor should it be synonymous with non-pneumococcal or non-bacterial pneumonia. Their view is that it merely describes a clinical pattern that can be seen with acute pneumonia caused by most aetiologic agents, and that pneumococcal and other bacterial pneumonias may, in some instances, present with clinical features not unlike those of *Mycoplasma pneumoniae* pneumonia. Similarly, patients with pneumonia due to one of the agents of the atypical pneumonia syndrome may have a clinical pattern identical with that of typical bacterial pneumonia. Likewise, this term has no value in describing pneumonia in elderly or immunocompromised patients as pneumonia due to the pneumococcus or other bacteria frequently present with atypical clinical features in such patients. A similar clinical picture may be produced by other agents such as influenza or

tuberculosis, or by non-infectious pulmonary conditions such as collagen-vascular disorders or malignancy (Yung et al., 1987).

Several features tend to be seen more often with the atypical pneumonia syndrome. These pneumonias usually have a subacute onset with a dry cough and accompanying constitutional symptoms, and tend to have patchy rather than the more usual lobar consolidation. There may be marked disparity between the clinical signs and chest X-ray features, and the white cell count may be normal. Because sputum tends to be scanty and show little in the way of organisms, the diagnosis may be missed unless the possibility of one of the atypical pneumonias is considered and special media used or specific serology done.

Of major clinical importance is the fact that pneumonias due to this atypical group do not respond to treatment with the usual antibiotics prescribed for bacterial pneumonias such as the penicillins or cephalosporins. However, mycoplasmal pneumonia is often a self-limited illness and complete recovery may occur in the absence of antibiotic therapy (Murray et al., 1975; Luby, 1991). Dual infections with more than one organism are well described, and additional infecting agents responsive to the above antimicrobials may be demonstrated together with mycoplasma or *Legionella,* most commonly *Streptococcus pneumoniae* or *Haemophilus influenzae* (British Thoracic Society, 1987; Lim et al., 1989).

Previous studies have shown that about 20% of community acquired pneumonias are caused by one of the agents responsible for the atypical pneumonia syndrome (Table 3). The role of *Chlamydia pneumoniae* in community acquired pneumonia is not known as there has been no commercially available test for it until recently. A recent survey at Groote Schuur Hospital has

shown that 35,9% of adults with community acquired pneumonia who were admitted to hospital had primary atypical pneumonia, the most common organisms being *Chlamydia pneumoniae* (20,7%), *Legionella pneumophila* (8,7%), and *Mycoplasma pneumoniae* (1,1%) (Maartens et al., 1994). However, as will be seen later, mycoplasmal infection occurs in cycles, and it is not known whether this study was performed during an epidemic or interepidemic period.

4. *MYCOPLASMA PNEUMONIAE*

4.1 Introduction

The mycoplasmas are the smallest known free-living micro-organisms with a particle diameter of about 300nm. They lack a cell wall thus making them deformable and able to pass through filters that exclude bacteria (Luby, 1991). The mycoplasma of chief importance in human disease is *Mycoplasma pneumoniae*. It attaches itself to the epithelial cell membrane via adherence protein or adhesin, but is, however, unable to penetrate the epithelial layer.

4.2 Epidemiology

Infections with *Mycoplasma pneumoniae* occur throughout the year with peaks during autumn and early winter (Luby, 1991). The disease is cyclical with epidemics occurring every 3 to 4 years. During these the incidence of disease doubles. Epidemics were demonstrated in the UK in 1974-1975, 1978-1979, and 1982-1983. The British Thoracic Society study (1987) of community acquired pneumonia was conducted during the 1982-1983 epidemic, while the Bristol study (White et al., 1981) extended from 1974 to 1980 and included 2 epidemic periods. Prevalence rates of mycoplasma as a cause of community acquired pneumonia during these studies were 18% and 14% respectively. In contrast, the study by Macfarlane et al. (1982) in Nottingham demonstrated only a 2% prevalence. This was conducted in 1980 and 1981 and so fell into an interepidemic period.

Spread is from person to person by infected respiratory droplets. Close contact is essential, and spread usually occurs within families or other closed populations such as college students or military recruits living in dormitories (Luby, 1991).

Infection may be asymptomatic, or may produce respiratory disease with or without pneumonia. Up to 35% of pneumonias treated on an out-patient basis are due to *Mycoplasma pneumoniae*, as are up to 18% of community acquired pneumonias requiring hospitalisation (Luby, 1991) (Table 3). In closed populations, the figure may be as high as 50% (Mansel et al., 1989). However, the true prevalence of *Mycoplasma pneumoniae* pneumonia is not known, and is probably underestimated because asymptomatic infections lead to a higher level of background exposure than is obvious from looking at pneumonia data (Levine & Lerner, 1978). Respiratory symptoms are minimal in about 77% who are infected with mycoplasma, while the disease is asymptomatic in a further 20% (Clyde, 1993). As a result, confirmatory evidence of pneumonia is usually not sought.

Fernald et al. (1975) detected serological evidence of mycoplasmal infection in 20 of 27 children who were asymptomatic, while Foy et al. (1983) were able to demonstrate a rise in antibodies suggestive of reinfection in 23 cases with previous mycoplasmal pneumonia. Only 3 of these (13%) had had symptoms of a pneumonia-like illness.

There is little information as to the prevalence of *Mycoplasma pneumoniae* pneumonia in the elderly, and the proportion of cases with mycoplasmal pneumonia who are older varies from one study to another (Table 4). However, it is evident that it is not common in older persons, and that the bulk of cases occur in persons under 40 years (Foy et al., 1970). Carr et al. (1991)

found only 1 case in 127 consecutive admissions (0,8%) with acute lower respiratory tract infection aged 65 years and older. Only 9% of the patients with *Mycoplasma pneumoniae* pneumonia reported by Marrie (1993) were 65 years or older, while only 18% (7/39) in the study by Ali et al. (1986) were over the age of 60 (Table 4). Mycoplasmal pneumonia is primarily a disease of schoolchildren and young adults with rates highest between 5 and 14 years (Foy et al., 1979). A smaller peak occurs in females in the 30 to 39 year age group, most of whom are mothers of schoolchildren (Foy et al., 1979).

The incubation period is 2 to 3 weeks. Despite appropriate antibiotic therapy, a nasopharyngeal carrier state may develop and mycoplasma may persist in the sputum for as long as 5 months following infection (Ali et al., 1986; Levine & Lerner, 1978; Foy, 1993). This means that in populations previously infected there are reservoirs of infection who are able to continue to spread the organism. This is prolonged in subjects with immune deficiency (Foy, 1993). The carriage rate in healthy populations varies, and tends to depend on whether the study is done during an epidemic or non-epidemic period. Throat swabs done on 2354 healthy schoolchildren showed that 3 (0,13%) were positive for mycoplasma (Foy et al., 1971). All 3 had had a recent mild respiratory illness. During epidemics in the military the carriage rate has been shown to be as high as 10%. Throat swabs done on healthy volunteers in Sweden who attended a clinic for vaccination for foreign travel showed a positivity rate of 13,5% during an epidemic period, but only 4,6% in a non-epidemic period (9,9% overall) (Gnarpe et al., 1992).

4.3 Immunology

The first antibodies to appear following infection with *Mycoplasma pneumoniae* are IgM immunoglobulins. They reach a peak some 10 to 30 days after the onset of symptoms, and then decline to become negative within about 3 months (Moule & Caul, 1987; Baum, 1995). IgM antibodies in the serum are thus indicative of acute or recent infection (Smith, 1986; Moule & Caul, 1987). However, in older persons IgM production is decreased or absent (Moule & Caul, 1987; Uldum et al., 1992), and may relate to the fact that the organism has been encountered before and that the current infection is due to reinfection rather than to a primary infection (Uldum et al., 1992).

IgG appears after IgM during the course of the first acute infection and may persist for as long as 3 years (Foy et al., 1983). Subsequent episodes of mycoplasmal infection are possible, and, during these, IgG levels rise (Jacobs, 1993). Thus, elevated levels of IgG may indicate previous infection (Smith, 1986) and may be detected in individuals who are well with no symptoms (Smith, 1986; Uldum et al., 1992). However, IgG may also suggest a current or recent reinfection as both IgG and IgA may rise in such circumstances without a corresponding rise in IgM (Jacobs, 1993).

The decline of serum antibody levels is more rapid in those who have milder disease (Foy et al., 1983), and is slower in young adults than in the very young (<5 years). Immunity is, however, not permanent and wanes with time. It is probably reinforced by subsequent episodes of infection which have been documented at 4 to 10 year intervals.

The well-known anti-I cold agglutinins are IgM antibodies directed against the I antigen on red cell membranes and fix complement at reduced temperatures (Levine & Lerner, 1978). They appear within the first 2 weeks after the onset of pneumonia in some 30 to 70% of cases (Luby, 1991; Murray et al., 1975).

4.4 Clinical manifestations

The manifestations of *Mycoplasma pneumoniae* infection may be respiratory or non-respiratory. Pneumonia is the most important and well-recognised, and is thought to occur in some 3 to 10% of individuals infected with *M. pneumoniae* (Mansel et al., 1989; Foy et al., 1971). The exact incidence is difficult to determine for, while the illness may be a severe one resulting in death from respiratory failure, it is usually mild, subtle and self-limiting leading fewer than 10% to seek medical attention (Mansel et al., 1989; Dular et al., 1987). About 5 to 10% require hospitalisation, although the rate may be as high as one third in some centres (Mansel et al., 1989).

Most patients who become infected with *Mycoplasma pneumoniae* are previously healthy, with no well-recognised conditions, other than Down's syndrome, leading to an increased susceptibility to mycoplasmal infection (Baernstein et al., 1965). In the study by Mansel et al. (1989) only 15,5% had pre-existing medical problems, although the illness may be more severe in those who have chronic lung disease (Cherry et al., 1971; McNamara et al., 1969). The mortality due to mycoplasmal pneumonia is low with rates varying from 0 to 5% (Table 5). This good prognosis may largely be due to the fact that it is the young and healthy who are most often affected.

4.4.1 Respiratory disease

In most clinically apparent cases of mycoplasmal infection there is a febrile upper respiratory tract illness without pneumonia. Sore throat is often the initial manifestation (Luby, 1991) and follows an incubation period of 12 to 14 days (Levine & Lerner, 1978). This is accompanied by constitutional symptoms of headache, fever, malaise and anorexia (Levine & Lerner, 1978). Otitis media and otitis externa may occur. Bullous myringitis is considered to be an infrequent manifestation, but was present in 18% in one series (Mansel et al., 1989).

Cough is the most prominent symptom in mycoplasmal pneumonia occurring in about 95% of cases (Mansel et al., 1989). It is usually non-productive, but small amounts of sputum may be produced. This is purulent in about a third (Murray et al., 1975). Gram-stain of the sputum reveals many polymorphonuclear leucocytes but no predominant organism (Murray et al., 1975; Luby, 1991), mycoplasma being too small to be detected by light microscopy (Mansel et al., 1989). This may be a useful pointer alerting the physician to suspect the diagnosis of *Mycoplasma pneumoniae* pneumonia (Murray et al., 1975). Haemoptysis is rare. Dyspnoea and wheezing may occur, and exacerbation of asthma and of chronic obstructive pulmonary disease are well described (Mansel et al., 1989). Pleuritic pain is uncommon (Murray et al., 1975).

Auscultation of the chest usually reveals crackles and wheezes, but clinical features of consolidation are generally absent (Luby, 1991; Mansel et al., 1989; Murray et al., 1975; Levine & Lerner, 1978). There is no characteristic pattern on chest radiograph. Patchy alveolar infiltrates or reticular infiltrates or both may be seen (Luby, 1991), with a predilection

for the lower lobes (Mansel et al., 1989). Lobar consolidation is uncommon (Luby, 1991; Mansel et al., 1989). Hilar adenopathy may be present, and small pleural effusions can be demonstrated in up to 20% in lateral decubitus views (Mansel et al., 1989).

4.4.2 Extrapulmonary manifestations

Cold agglutinins are the most common extrapulmonary manifestation observed (Ali et al., 1986), and may cause haemolysis although this is seldom clinically significant. Characteristically, the haemolysis occurs 2 or 3 weeks after the onset of symptoms, and coincides with recovery from pneumonia and the peak cold haemagglutinin titre (Murray et al., 1975). Severe haemolytic anaemia is rare, and may be associated with haemoglobinuria, renal failure, and even death (Levine & Lerner, 1978).

Neurologic manifestations were first described in the initial report of primary atypical pneumonia in 1938, and occur in about 7% of patients with mycoplasmal infection requiring hospitalisation (Ali et al., 1986; Levine & Lerner, 1978). The features include aseptic meningitis, encephalitis, brachial plexus neuropathy, transverse myelitis, mononeuritis multiplex, Guillain-Barré syndrome, and bilateral sensorineural hearing loss (Luby, 1991; Murray et al., 1975; Levine & Lerner, 1978). Neurologic symptoms usually have their onset within 14 days of the respiratory symptoms, and do not correlate with the severity of the mycoplasmal infection. Recovery is usually complete, but may take as long as 5 months. The development, severity and duration of neurologic features do not appear to be influenced by antibiotic therapy (Murray et al., 1975).

Cardiac disease occurs in about 4,5% with mycoplasmal infection (Ali et al., 1986; Pönkä, 1979). Rhythm disturbances, as well as ST-T wave changes on ECG, may occur. Pericardial effusions have been described, and, rarely, dilated cardiomyopathy with left heart failure (Luby, 1991).

There may be hepatomegaly (Luby, 1991) together with mild elevation of transaminases and alkaline phosphatase (Levine & Lerner, 1978). Splenomegaly has been described, as have glomerulonephritis and acute pancreatitis (Luby, 1991). Generalised lymphadenopathy is rare (Ali et al., 1986; Murray et al., 1975). Gastrointestinal symptoms of anorexia, nausea, vomiting and diarrhoea are common (Murray et al., 1975).

Skin rashes are reported in up to 25% (Murray et al., 1975; Levine & Lerner, 1978), and include macular, petechial, morbilliform, and papulo-vesicular rashes, as well as erythema nodosum and urticaria (Murray et al., 1975). Erythema multiforme may occur, and the Stevens-Johnson syndrome has been reported in up to 4% (Ali et al., 1986). Dermatologic manifestations develop within 2 weeks of the onset of respiratory illness, and may persist long after the pulmonary features have resolved (Murray et al., 1975). It has been suggested that certain antibiotics may precipitate the development of rashes in mycoplasmal infection in much the same way that ampicillin does in infectious mononucleosis (Ali et al., 1986; Levine & Lerner, 1978).

Nonspecific myalgias and arthralgias occur in 15 to 45% (Murray et al;., 1975; Cassell, 1981). There may be an inflammatory arthritis mainly involving large joints which is migratory and polyarticular (Ali et al., 1986; Murray et al., 1975). This coincides with the acute illness, is

transient, and resolves with recovery from the respiratory infection. The joint manifestations may pose a diagnostic problem causing confusion with acute rheumatic fever or rheumatoid arthritis.

4.5 Clinical course

Mycoplasmal pneumonia is usually self-limited, and most patients make a complete recovery (Murray et al., 1975; Luby,1991). Fever, headache and malaise resolve in 3 days in untreated cases, whereas chest signs take longer to disappear paralleling radiological clearing. X-ray features may resolve in 10 to 21 days, but complete resolution can take up to 6 weeks (Murray et al., 1975). There have been reports of chronic pulmonary sequelae with progressive fibrosis, bronchiectasis, bronchiolitis obliterans or organising pneumonia following mycoplasmal pneumonia (Luby, 1991). Although appropriate antibiotic therapy does not eradicate the organism from the respiratory tract, the duration of symptoms is decreased and resolution of radiological abnormalities is accelerated (Murray et al., 1975).

The disease is rarely fatal, but may occasionally be serious and life threatening (Table 5). In the British Thoracic Society study (1987) the mortality rate of those patients with *Mycoplasma pneumoniae* pneumonia was 4.9%. All were given appropriate antibiotics after admission, although not before.

4.6 Mycoplasmal pneumonia in the elderly

The fact that the elderly have more chronic disease than younger patients does not appear to put them at greater risk for developing mycoplasmal pneumonia. It is not known whether the complication rate increases with age, nor whether mortality is increased by age, although neither seems to be the case. No studies have assessed long-term morbidity, although it would appear that complete recovery is the norm, even in the elderly.

Marrie (1993) reported on 64 patients with mycoplasmal pneumonia who required hospitalisation. Of these, 58 (90,6%) were aged 64 or younger (mean 37,3 years), while 6 (9,4%) were 65 or older (mean 78,3 years). The mean number of underlying diseases was more than three times greater in the older group (3,0 as compared with 0,9), and the mean length of hospital stay was two and a half times greater (30 as compared with 11,7 days). Despite these features which would suggest the contrary, the proportion who developed complications was similar in the 2 groups: 10 (17,2%) in the younger group and 2 (17%) in the older group. These included respiratory failure requiring ventilation, pulmonary haemorrhage, haemolysis, thrombocytopenia, cerebro-vascular accident, and Guillain-Barré syndrome. In this study only 1 death occurred, and this was in a 51 year old man with Shy-Drager syndrome who had recovered from his pneumonia and died from his underlying disease.

There were 39 patients with mycoplasmal pneumonia in the study by Ali et al. (1986). Of these 7 (18%) were older than 60 years. Only 3 had significant complications: a teenage boy developed Stevens-Johnson syndrome, and a 67 year old man developed sensorineural

deafness. Both recovered. The third was a 38 year old woman with Down's syndrome who died. She had severe multilobe pneumonia, pleural effusion, pericardial effusion, and haemolytic anaemia.

Mansel et al. (1989) report on 148 patients with *Mycoplasma pneumoniae* pneumonia, 14 (9,5%) of whom were older than 40. Prior or co-existing medical problems were present in 23 (15,5%) and 49 (33%) developed extrapulmonary manifestations. Unfortunately, the ages of these subjects are not mentioned. Complications were rare with 1 man (age not given) developing adult respiratory distress syndrome from which he made an uneventful recovery. The only death was in a 3 month old baby with mixed immunodeficiency who died following open lung biopsy and in whom concurrent infection with both *Mycoplasma pneumoniae* and *Nocardia asteroides* was demonstrated.

These studies would suggest that, despite the fact that older patients are more likely to have underlying disease, their complication rate and mortality from mycoplasma pneumonia is no greater than in younger patients. They may, however, take longer to recover and may require a longer period of hospitalisation. The fact that these studies were conducted in hospitalised patients may have made the numbers of elderly disproportionately high, as older patients and those with co-morbid illness are more likely to be hospitalised than are younger patients with disease of the same severity. The lack of demonstration of more adverse outcomes in the older patients, therefore, underlines even more strongly the relatively benign nature of this disease.

4.7 Diagnosis

Most authorities would agree that culture of mycoplasma in the sputum constitutes definite evidence for current infection (Ali et al., 1986; Foy et al., 1971; Levine & Lerner, 1978). However, Gnarpe et al. (1992) in Sweden were able to demonstrate that 9,9% of healthy adults attending a clinic for vaccination for foreign travel had positive mycoplasmal cultures from throat swabs, although very few had any history of recent respiratory infection.

Serological diagnosis of acute infection is based on the demonstration of a fourfold or greater rise in antibody titre between paired acute and convalescent sera using any of the available serologic tests (British Thoracic Society, 1987). A single titre ≥4 (British Thoracic Society, 1987) or >16 (Maartens et al., 1994) for mycoplasmal IgM is considered definite evidence of acute infection. A single titre in a convalescent specimen ≥64 for the mycoplasmal specific IgG indirect fluorescent antibody test is considered evidence of probable infection (Maartens et al., 1994).

Cold haemagglutinins (anti-I IgM) appear during the first or second week in mycoplasmal infections, but are found in only 30 to 70% of cases (Luby, 1991; Murray et al., 1975) so that a negative test is not of much value (Jacobs, 1993). A single titre ≥64 or a fourfold rise in paired sera ≥5 days apart is considered evidence of acute infection. A low cold agglutinin titre <64 may be due to infection with viruses such as adenovirus, respiratory syncytial virus, mumps, influenza or infectious mononucleosis, as well as collagen vascular disorders and myeloma.

4.8 Treatment

Treatment of infection with *Mycoplasma pneumoniae* is often empiric and based on clinical suspicion before the diagnosis is confirmed. Antibiotics are not usually necessary for mycoplasmal upper respiratory infections. However, although *Mycoplasma pneumoniae* pneumonia is a self-limiting illness which is seldom life-threatening, effective antibiotic therapy may markedly decrease the duration of the illness and, in doing so, decrease spread.

Erythromycin and tetracycline are the agents that have been most extensively used against *Mycoplasma pneumoniae*. They are equally effective clinically and have come to be regarded as the drugs of choice (Yung et al., 1987; Rasch & Mogabgab, 1965), although neither is mycoplasmacidal (Mansel et al., 1989). Because mycoplasma lacks a cell wall, it is resistant to the beta-lactam antibiotics such as the penicillins and the cephalosporins. Both erythromycin and tetracycline have been shown to shorten the duration of fever and hospitalisation, and to hasten the resolution of radiological changes (Rasch & Mogabgab, 1965). They do not, however, eradicate the organism from the respiratory tract, and cultures of the nasopharynx and sputum may remain positive for weeks to months (Smith et al., 1967). This may relate to the fact that, although mycoplasma is an extracellular organism and adheres to the endobronchial epithelium, it is able to reside intracellularly as well. The efficacy of antibiotics in controlling the extrapulmonary manifestations is not known (Mansel et al., 1989; Cassell & Cole, 1981; Murray et al., 1975).

Most patients become afebrile within 48 hours of commencing therapy. There is no consensus on the optimal duration of therapy for *Mycoplasma pneumoniae* pneumonia, but most treat for

2 to 3 weeks to avoid relapse which may occur in 10% (Cotton et al., 1987; Yung et al., 1987; Baum, 1993). The total daily dose of erythromycin or tetracycline for adults is 1-2gm. Erythromycin has a high incidence of gastro-intestinal side-effects and may be poorly tolerated. The use of tetracycline is precluded in young children because of its adverse effect on developing teeth and bone. Doxycycline is better tolerated than tetracycline, and should be given in a dose of 100-200mg per day (Yung et al., 1987). Therapeutic failures with both erythromycin and tetracycline have been reported, and it is suggested that therapy with the alternate agent be instituted if there has been no improvement within 5 to 7 days of therapy (Ford et al., 1980).

The newer macrolides, clarithromycin and azithromycin, have also been shown to be active against mycoplasma. They have several advantages over erythromycin, with better oral absorption and fewer gastro-intestinal side-effects (Neu, 1992; Wood, 1991; Peters & Clissold, 1992).

Mycoplasma pneumoniae is susceptible to the quinolones, although they are expensive and not as effective as the macrolides (Waites et al., 1988). They are also relatively contra-indicated in children due to their adverse effect on weight-bearing joints in the young.

Steroids have been used in conjunction with antibiotic therapy and appear to be useful in patients with severe pneumonia and erythema multiforme. However, controlled prospective studies are needed to assess their true value (Levine & Lerner, 1978).

5. *LEGIONELLA PNEUMOPHILA*

5.1 Introduction

Legionella pneumophila was probably first isolated in 1947, when the organism was recovered from the blood of a patient with a febrile respiratory illness using guinea pig inoculation (McDade et al., 1979). An outbreak was associated with a meat packing plant in 1957 (Osterholm et al., 1983) and another in a Washington psychiatric hospital in 1965 (Eickhoff, 1979). However, it was not until July 1976 when an outbreak occurred in Philadelphia during a convention of the American Legion that attention was drawn to the infection and it was given the name Legionnaires' disease (Fraser et al., 1977). The causative organism was isolated from the lung tissue of four fatal cases in January 1977 (McDade et al., 1977), and was subsequently named *Legionella pneumophila* (Brenner et al., 1979).

5.2 Microbiology

Legionella pneumophila is a fastidious non-acid-fast bacillus which is an obligate aerobe and stains very poorly with the Gram stain. It does not grow on standard bacteriologic media (McDade et al., 1977; Isenberg, 1979), but will grow on buffered charcoal yeast extract agar. These features cause some difficulty in diagnosis using routine techniques.

5.3 Epidemiology

The *Legionella* species are ubiquitous water micro-organisms which grow best in stagnant water, especially if it is warm (Edelstein & Meyer, 1984). They have been isolated from many aquatic sources including fresh water lakes, plumbing fixtures, air conditioning systems, and distribution systems for drinking water (Edelstein & Meyer, 1984; Nguyen & Yu, 1991).

Both sporadic and epidemic forms of infection with *Legionella* occur, the latter being described in public buildings such as hotels or hospitals where infection has, in some instances, been traced to a point source (England et al.,1981). An association with travel and with exposure to construction and excavation has been noted. Spread is by aerosolisation of contaminated water via air conditioning systems, showerheads or nebulisers (Meyer, 1984). In an outbreak in a Johannesburg hospital (Strebel et al., 1988) ventilators were thought to have played a role in the spread of infection. Person to person spread does not occur (Nguyen & Yu, 1991). There appears to be seasonal variation in *Legionella* infection with a summer-autumn predominance (Eickhoff, 1979). The reason for this is uncertain, one explanation given being that air conditioning systems are used more extensively in summer (England et al., 1981).

Infection with *Legionella* may occur at any age, but is more common in the elderly with a peak incidence over the age of 60 (Cotton et al., 1987). It is exceedingly uncommon in children. Other than age, risk factors for infection include male sex, smoking, alcoholism, diabetes, chronic cardiopulmonary disease, and immunosuppression (Davis et al., 1981; Fraser et al., 1977; Gump et al., 1979; Eickhoff, 1979). The attack rate in recipients of renal or bone

marrow transplants is especially high (Edelstein & Meyer, 1984). However, patients with neutropenia or AIDS do not appear to have an undue predilection for the disease (Nguyen & Yu, 1991).

The reported prevalence of *Legionella* infection varies from one centre to another. It is the causative agent in 2 to 23% of community acquired pneumonias requiring hospitalisation (Table 3), being second only to *Streptococcus pneumoniae* in several Spanish studies (Blanquer et al., 1991; Pachon et al., 1990; Rello et al., 1993). The rates within an area may also vary, and in Nottingham, UK in 1980-1981 *Legionella* pneumonia constituted 15% of community acquired pneumonias in adults (Macfarlane et al., 1982), despite a low background antibody titre in the population and despite no apparent evidence for clustering emanating from a single source (Macfarlane et al., 1982; Macrae et al., 1979). This high yield was attributed to the fact that *Legionella* was vigorously sought even in patients who were not seriously ill. Convalescent sera from all subjects were tested, thus enabling a diagnosis to be made which might otherwise have been missed. The high prevalence of *Legionella* in Nottingham has not persisted, however, and in the British Thoracic Society study (1987), which was conducted in 1982-1983, only 2 patients (5%) from Nottingham were shown to have *Legionella*. The Bristol study (conducted from 1974 to 1980) showed a prevalence of only 1,5% (White et al., 1981). *Legionella* was not sought in the early years of this particular study as it only became recognised as a distinct entity following the outbreak in Philadelphia in 1976 (Fraser et al., 1977), and sera for testing for antibodies to *Legionella* only became available from that time onwards (White et al., 1981). Similarly, 9% of cases of community acquired pneumonia admitted to Groote Schuur Hospital during 1987-1988 had *Legionella pneumophila* pneumonia (Maartens et al., 1994), but no cases had been identified in the same

hospital in a 6 month period during 1980 (Prout et al., 1983). The prevalence of nosocomial infections due to *Legionella* may be as high as 30% (Meyer, 1984).

5.4 Clinical manifestations

Legionella pneumophila is best known as the cause of Legionnaires' disease, an acute pneumonic illness. However, together with other species of the genus *Legionella*, it may also cause a non-pneumonic illness, Pontiac fever, or may be responsible for subclinical infection (Glick et al., 1978; McDade et al., 1977).

Silent or subclinical disease is probably the most common form of *Legionella pneumoniae* infection (Marik, 1989), and this may be inferred from the presence of antibodies to *Legionella pneumophila* in individuals who are totally asymptomatic (Kirby et al., 1980).

Pontiac fever is an acute self-limiting febrile illness that derives its name from the first recognised outbreak which occurred in the health department in Pontiac, Michigan in 1968 (Glick et al., 1978). It is a flu-like illness with high fevers, myalgia, headache and malaise, and develops 1 to 2 days post exposure. Pneumonia does not occur (McDade et al., 1977; Kirby et al., 1980), and complete recovery within 1 week is the norm. Diagnosis is based on documentation of seroconversion, as the organism has never been isolated from affected individuals.

5.4.1 Legionnaires' disease

The incubation period for Legionnaires' disease is 2 to 10 days (Swartz, 1979). Early symptoms are those of an influenza-like illness with malaise, weakness and lethargy. High fevers are typical, frequently accompanied by rigors. Unlike mycoplasmal pneumonia, upper respiratory tract symptoms are usually absent (Tsai et al., 1979). Cough is present in 87% (Kirby et al., 1980), but is not a prominent feature early in the disease. It is usually non-productive, but small amounts of sputum may be produced in 50% which may be purulent or even bloody (Tsai et al., 1979; Edelstein & Meyer, 1984). Chest pain, usually pleuritic, is present in about a third of patients (Swartz, 1979).

Clinical findings in the chest are unimpressive, and usually reveal scattered crackles or wheezes with the later development of areas of consolidation (Tsai et al., 1979; Edelstein & Meyer, 1984). Radiologic manifestations are variable, initially being unilateral in the majority of cases (Swartz, 1979). Patchy alveolar infiltrates are most commonly seen, progressing to consolidation in about 70% (Nguyen & Yu, 1991). This may involve upper or lower zones, or may become bilateral (Edelstein & Meyer, 1984). Multilobar involvement has been reported in 65% (Swartz, 1979). Small pleural effusions are present in a third of patients (Nguyen & Yu, 1991). Cavitation is unusual (Swartz, 1979). Radiologic features tend to progress even in the face of adequate treatment (Muder et al., 1987), with radiologic improvement usually lagging behind clinical improvement and taking up to 4 months for complete clearing to occur (Swartz, 1979).

5.4.2 Extrapulmonary manifestations

These features are believed to be the result of bacteraemic dissemination. Gastrointestinal symptoms are a prominent feature in the early stages, with watery diarrhoea in about 40% (Tsai et al., 1979; Kirby et al., 1980). Abdominal pain may be present, and nausea and vomiting occurs in about 25% (Tsai et al., 1979; Kirby et al., 1980). Mild elevations of serum transaminases are common (Tsai et al., 1979).

Abnormalities of the central nervous system occur in a third of patients (Kirby et al., 1980). Headache is seen in 40% (Kirby et al., 1980), and confusion in 30% (Cotton et al., 1987). Other features include agitation, hallucinations, stupor, amnesia, grand mal seizures, dysarthria, ataxia, and peripheral neuropathy (Edelstein & Meyer, 1984).

Renal abnormalities range from mild elevations of the urea and creatinine to frank renal failure (Tsai et al., 1979). Cardiac involvement has been described with the development of pericarditis or endocarditis, and episodes of culture negative endocarditis should prompt a search for *Legionella* (Nguyen & Yu, 1991). Relative bradycardia is common and is found in about 60% (Kirby et al., 1980).

5.5 Diagnosis

Usually the diagnosis of acute *Legionella* infection is made serologically, the indirect fluorescent antibody test being the most widely used (Cotton et al., 1987; Edelstein & Meyer, 1984; Ratshikhopha et al., 1990; Marik, 1989). A fourfold or greater rise in antibody titre to a level of at least 128 together with a compatible clinical picture is regarded as diagnostic (Wilkinson, 1982; Ratshikhopha et al., 1990; Cotton et al., 1987; Marik, 1989) with sensitivities and specificities of 70 and 95% respectively (Wilkinson et al., 1983). A single titre of at least 256 is considered to be presumptive evidence of infection at an unknown time, but is not diagnostic because of the high level of subclinical or mild infection that may exist in the particular population from which the patient comes (Wilkinson et al., 1982).

The immunological response to *Legionella* infection may be with IgG, IgM and IgA singly or in various combinations. IgG and IgM titres may remain elevated for several years, but IgA levels are not sustained. For this reason, polyimmunoglobulin conjugates (total immunoglobulin titres) are used in the indirect fluorescent antibody test instead of measuring titres of individual immunoglobulin classes (Wilkinson et al., 1982).

Antibody titres generally begin to rise by the third week after onset, a fourfold rise having occurred in most patients by week 6 (Kirby et al., 1980). However, about 20 to 30% with Legionnaires' disease remain seronegative (Edelstein & Meyer, 1984). It is possible that testing later in convalescence may demonstrate an antibody response, or that disease in these patients is caused by a serogroup not detected by the antigen used in the test (Kirby et al., 1980). Antibody titres may remain elevated for at least 2 years (Lattimer et al., 1979; Tsai &

Fraser, 1978), even after appropriate antibiotic therapy, making it difficult to distinguish present from past illness (Nguyen & Yu, 1991; Kirby et al., 1980). A further confounder is the fact that immunofluorescent antibody titres are not entirely specific, and cross-reactivity may occur with *Pseudomonas* and other Gram-negative bacteria, as well as *Mycoplasma pneumoniae* and *Chlamydia psittaci* (Kirby et al, 1980).

Legionella may also be cultured from respiratory secretions, but it is a slow growing and fastidious organism requiring special media (Edelstein & Meyer, 1984). The yield in sputum is less than 40%, but may be higher from transtracheal aspiration (Marik, 1989). Direct immunofluorescent examination for *Legionella* antigen in sputum or other body fluids or tissue is highly specific (99,9%) but only moderately sensitive (70-75%).

5.6 Treatment

Legionella pneumonia is a much more severe disease than mycoplasmal pneumonia with most patients requiring hospitalisation. The mortality rate is 15 to 20% (Edelstein & Meyer, 1984), but rates as high as 67% have been reported (White et al., 1981) (Table 5). The mortality in nosocomial infections may approach 50%, especially if antibiotic therapy is started late (Yu, 1995). Mortality is greater in patients who are older or who have chronic underlying disease, particularly chronic bronchitis or emphysema (England et al., 1981). Early diagnosis is difficult (British Thoracic Society, 1987) further contributing to the adverse outcome. The mortality rates in immunosuppressed patients are even higher with rates up to 80% being recorded (Edelstein & Meyer, 1984). It is thus important that antibiotics active against *Legionella* be

started early in all patients with community acquired pneumonia who are seriously ill and in whom a diagnosis of *Legionella* is considered.

Erythromycin was the drug of first choice in *Legionella* pneumonia (Kirby et al., 1980; Gump et al., 1979), although this may be changing with the advent of newer agents. It was used as empiric therapy in the early outbreaks of Legionnaires' disease with a fourfold decrease in fatality rates (Edelstein & Meyer, 1984). The mortality rate in those patients who did not receive erythromycin was 23 to 55%, while in those in whom it was used the rate was 6 to 13% (Beaty et al., 1978; Tsai et al., 1979; Kirby et al., 1980). Its activity against *Legionella* may be explained by the fact that erythromycin is concentrated within alveolar macrophages and polymorphonuclear leucocytes (Johnson et al., 1980). Erythromycin should be given in a daily dosage of 2gm orally or 4gm IV. However, the gastro-intestinal disturbance seen with *Legionella* may compromise absorption of the oral form. As a result, it may be necessary for initial treatment to be given intravenously, especially in those patients who are severely ill, and for oral therapy to be commenced only once clinical improvement occurs, usually within 3 to 5 days (Yu, 1995). Treatment should be continued for at least 2 to 3 weeks to decrease the likelihood of relapse (Swartz, 1979; Yu, 1995). A longer duration of therapy is appropriate for immunosuppressed patients.

The newer macrolides (azithromycin, clarithromycin and roxithromycin) have superior *in vitro* activity and improved pharmacokinetics when compared to erythromycin. However, they are much more costly and clinical trials of efficacy have yet to be performed (Yu, 1995). Clarithromycin appears to be the drug most active against *Legionella* (Peters & Clissold, 1992). It achieves higher concentrations than erythromycin in tissues such as the lung, and its

ability to penetrate cells is an advantage in treating organisms which proliferate within cells as *Legionella* does (Peters & Clissold, 1992; Neu, 1992). It has also been shown to have some bactericidal activity against *Legionella* (Peters & Clissold, 1992).

Tetracycline has also been shown to decrease mortality, but the results have been inconsistent (Woodhead, 1992; Kirby et al., 1980; Cotton et al., 1987). Nguyen and Yu (1991) have suggested that their high lipid solubility and twice daily dosage may give doxycycline or minocycline an advantage over conventional tetracycline.

In *Legionella* pneumonia, the organism has been shown to be concentrated within the lung macrophage (Nguyen & Yu, 1991). Rifampicin has been shown to be potent and highly effective against *Legionella*, no doubt due in part to the fact that it is able to penetrate the macrophage and achieves a high concentration within the lung (Thornsberry et al., 1978; Liebers et al., 1989; Moffie & Mourten, 1988). However, because of the danger of developing resistance, rifampicin should not be used alone, but should be reserved for use in combination in patients who are seriously ill (Kirby et al., 1980).

The fluoroquinolones, ofloxacin and ciprofloxacin, are active against *Legionella*, and patients unresponsive to erythromyin have been successfully treated with ciprofloxacin. However, there is very little clinical data to support their use (Hooper & Wolfson, 1991; Unertl et al., 1989).

There is limited experience with agents such as trimethoprim-sulfamethoxazole and imipenem, and reports are anecdotal only (Farrell et al., 1985).

Mortality rates are higher in patients who are immunosuppressed. Steroids have no place in the management of *Legionella*, and should be stopped wherever possible in patients already receiving these agents (Tsai et al., 1979).

6. ERYTHROMYCIN AND THE NEWER MACROLIDES

Erythromycin belongs to the macrolide group of antibiotics (Washington & Wilson, 1985) and is produced by *Streptomyces erythraeus*. It is bacteriostatic, and binds to the 50S subunit of the bacterial ribosome, thus inhibiting protein synthesis (Dollery, 1991). Its spectrum of antibacterial activity is similar to that of penicillin giving it a particular role in patients with penicillin allergy. In addition, it has antibacterial activity against *Legionella*, mycoplasma and chlamydia.

Both oral and parenteral forms exist. Oral absorption is inconsistent, and depends on various factors, such as the form used, gastric acidity, and the presence of food in the stomach. Once absorbed, it is extensively distributed into most tissues and body fluids, but is unable to penetrate the CSF. It is highly protein-bound (>70%) (Washington & Wilson, 1985). A small percentage is excreted unchanged in the urine (2,5% of oral form and 15% of intravenous form). The remainder is partially metabolised in the liver by demethylation. Most is concentrated and excreted in active form in the bile.

Erythromycin is responsible for several important drug interactions, and these may be particularly severe in older people or those with chronic disease. It inhibits the hepatic microsomal enzymes and thus has the potential to cause a rise in serum levels and increased activity of various drugs, including theophylline (Iliopoulou et al., 1982), carbamazepine (Wroblewski et al., 1986), warfarin (Bartle, 1990), and digoxin (Lindenbaum et al., 1981) with the risk of toxicity or haemorrhage.

Gastrointestinal intolerance is prominent, with frequent complaints of nausea, vomiting, diarrhoea, abdominal pain or cramps. This may occur with both oral and IV preparations, particularly with doses greater than 4gm per day. A dose-related increase in serum transaminases may occur, which may recur on rechallenge with the drug.

An immunologically mediated cholestatic jaundice is well recognised but rare and manifests with abdominal pain, nausea, anorexia and fever. It may be associated with skin rashes, urticaria, eosinophilia, and an elevation in liver enzymes. Liver toxicity has been most commonly reported with the estolate form, but this may reflect its more widespread use rather than any greater toxic potential. Symptoms usually begin after 10 to 20 days of treatment, and disappear within days of ceasing therapy.

Use of the intravenous form may cause local pain and irritation, or even thrombophlebitis. Intramuscular injection is not recommended as it is extremely painful, and sterile abscesses may occur.

Reversible hearing loss is a rare complication of erythromycin therapy. It has been observed most often in patients given 4gm or more daily, especially in the presence of renal failure (Washington & Wilson, 1985; van Marion et al., 1978).

Allergic reactions occur rarely, and include fever, rash, eosinophilia and joint pain.

Erythromycin has been in use for more than 40 years, and is considered to be an extremely safe agent (Neu, 1992). However, in the last 10 or 15 years several newer macrolides have

been developed which do have some advantages over erythromycin (Neu, 1992; Peters & Clissold, 1992; Wood, 1991). These include clarithromycin, azithromycin, roxithromycin, flurithromycin, and dirithromycin. The new macrolides are more stable in acid and are thus better absorbed from the gastro-intestinal tract. Their tissue and intracellular concentrations are higher, and they have longer half-lives permitting longer dosing intervals than those required with erythromycin. More important, however, is the improved microbiological activity of the newer agents. Both clarithromycin and azithromycin inhibit *Mycoplasma pneumoniae*, *Legionella pneumophila* and *Chlamydia pneumoniae* at lower concentrations than does erythromycin. They also have activity against *Haemophilus influenzae*, a property which is lacking in erythromycin, and are active against *Mycobacterium avium*. In addition, azithromycin is active against *Toxoplasma gondii* and *Borrelia burgdorferi*. These drugs are also better tolerated as they have fewer gastro-intestinal side-effects.

D. STUDY

1. MOTIVATION

The mortality associated with community acquired pneumonia is significant, particularly in elderly subjects (Tables 1 & 2). Institution of an appropriate antibiotic at an early stage is essential if this high mortality is to be reduced. Verghese and Berk (1983) have demonstrated improved survival rates in those in whom initial therapy was appropriate as compared with those in whom the use of an appropriate agent was delayed. They define "appropriate" therapy as that antibiotic or combination of antibiotics which is begun within 24 hours and to which the organism is shown to be sensitive. This requires an accurate prediction as to the most likely aetiologic agent.

A knowledge of local prevalence rates of the different microbial agents causing pneumonia would permit empiric therapy to be tailored to local conditions. This is important for, while a second-generation cephalosporin has been recommended as the most suitable first-line agent for the treatment of community acquired pneumonia in the elderly in South Africa (SA Pulmonology Society, 1996), if *Legionella* or mycoplasma comprised a significant proportion of causes of pneumonia, it would be prudent to add erythromycin or one of the newer macrolides. In contrast, the addition of erythromycin as a routine would be unnecessary if local prevalence rates were low and infection with these organisms was not expected to occur sufficiently frequently to justify the additional expenditure. There is little information as to the prevalence of *Legionella* or mycoplasma infection in the elderly in South Africa. It would

therefore be helpful to know the level of exposure to these organisms in elderly subjects in our community.

2. AIM

To provide information as to the most appropriate first-line antibiotic therapy for community acquired pneumonia in the elderly in South Africa.

3. OBJECTIVE

To determine the prevalence of *Legionella* and mycoplasma seropositivity in the elderly in old age homes in Cape Town.

4. SUBJECTS AND METHODS

4.1 Study population

All the residents of four old age homes in the Cape Peninsula were invited to participate in this study. Subjects aged 60 years and older were eligible for inclusion. The only subjects who were excluded were those who refused to participate, or those who were willing but from whom blood could not be obtained for technical reasons. No person was excluded on the basis of previous or current medical problems or drug therapy.

The four old age homes chosen were all subsidised homes belonging to the Cape Peninsula Organisation for the Aged, and were chosen largely because of the fact that they were fairly close to Groote Schuur Hospital, and therefore easily accessible. In order to make the study sample as representative as feasibly possible, an attempt was made to include subjects from all population groups in the Cape Peninsula, including those who have historically been disadvantaged. However, at the time that the study was undertaken, old age homes were segregated accorded to colour, and there were no old age homes for black people. The homes visited in this study thus comprised two which housed white residents only, while the other two housed so-called coloured people.

4.2 Methods

Baseline information (including demography, health status, smoking history, functional status and current therapy) was obtained for each participant using the medical records as well as information from the nursing staff. The data sheet is shown in Appendix I.

Blood was taken from each subject and, after separation of the serum, was stored at -20^{0}C until antibody titres to *Legionella* and mycoplasma could be determined in batches.

The detection of antibodies to *Mycoplasma pneumoniae* was performed using an indirect fluorecent antibody technique (Zeus Scientific Inc., New Jersey, USA). Species specific membrane antigen was incubated with the serum to be tested, and antibody was demonstrated by staining with fluorescein-labelled anti-human antibody. A single IgG titre of 32 or greater was considered to indicate previous infection, while a titre of 64 might be indicative of current

or recent infection. IgM antibodies were also sought, and these were regarded as indicative of current or recent infection only. A single titre of 32 or greater was considered to be significant.

The presence of antibodies to *Legionella pneumophila* was sought using an indirect fluorescent antibody test (Zeus Scientific Inc., New Jersey, USA). The assay uses heat-killed *Legionella* bacteria (*L. pneumophila* groups 1 - 4) as the substrate antigen and polyvalent fluorescein-labelled anti-human globulin as the antibody indicator. A single titre of 128 or greater was considered to be positive and to indicate previous infection with *Legionella*. A titre of 256 or greater is presumptive evidence of acute or recent infection.

4.3 Ethical considerations

Approval for the study was obtained from the UCT Ethics and Research Committee, as well as from the Medical/Nursing Advisory Committee of the Cape Peninsula Organisation for the Aged, the managers of the four old age homes included in the study, and from the doctors providing medical care for the residents of the homes. Confidentiality was ensured.

Written consent was obtained for all subjects, either from the subject him/herself, or from a relative, or from the Matron in charge of the old age home. Because this study required simply that a single blood specimen be taken, it was not felt necessary to contact a family member in all cases where the subject could not give consent.

4.4 Sample size

As all residents of the 4 old age homes who met the criteria were included, sample size was not determined prior to the study. This was, however, done later as an exercise using the Statcalc function of Epi Info Version 5.

5. RESULTS

There were 766 residents in the 4 homes, and 677 (88,4%) participated in the study. Of these, 174 were males (25,7%) and 503 were females (74,3%), with a mean age of 78,1 years (range 60-98 years). The non-respondents were too young (<60 years), or refused to participate, or were not in the home during that period because they were away on holiday or in hospital, or a blood specimen could not be obtained.

5.1 *Mycoplasma pneumoniae*

There were 17 participants (17/677 = 2,51%) with antibodies to *Mycoplasma pneumoniae* (Table 6). Of these 8 (8/17=47,06%) had IgG antibodies only and 1 (1/17=5,88%) had IgM antibodies only, while the remaining 8 (8/17=47,06%) had both IgG and IgM. This meant that IgG was present in 16 participants (16/677=2,36%) and IgM in 9 (9/677=1,33%).

The IgM titres were low with 1 participant (1/9=1,11%) having a titre of 16, while the titre in the remaining 8 (8/9=88,89%) was 8. The IgG titres were also low with 3 participants (3/16=18,75%) having titres of 64, 12 (12/16=75%) having titres of 32 and the remaining 1 (1/16=6,25%) having a titre of 8. Each of those who were positive for both IgM and IgG had an IgM titre of 8. The remaining participant who was IgM positive had a titre of 16.

IgM positivity was confined to 2 of the 4 old age homes where the investigation took place, there being 5 positives in one of the homes and 4 in the other. All except 3 of those who were IgG positive were in the same 2 homes.

5.2 *Legionella pneumophila*

Antibodies to *Legionella pneumophila* were demonstrated in only 9 (1,33%) participants (Table 7), 7 (78%) of whom were female and 2 (22%) of whom were male. There was no clustering of positive sera with 3 each coming from homes 1 and 2, another 2 from home 3, and the remaining 1 from home 4. In 6 (0,89%) the titre was 128, while in 1 (0,15%) it was 256, and in the remaining 2 (0,29%) it was 512. The ages of those with positive titres ranged from 68-85, with a mean of 77,1 years (compared with the sample mean of 78,1 years).

There were 4 with positive *Legionella* serology who were smokers, while 1 was an ex-smoker, and the remaining 4 had never smoked. Chronic obstructive airways disease had been diagnosed in 3, all of whom were either current or previous smokers. There were 2 subjects with a history of congestive heart failure, but none with renal disease or diabetes. A single participant, who did not have a history of chronic obstructive airways disease, had recently had a pneumonic illness which had not required hospitalisation, and for which she was receiving amoxycillin at the time of the survey. The titre in this subject was 256. There were 2 subjects with a titre of 512. Neither had evidence to suggest a recent pulmonary infection. One was a smoker with chronic obstructive airways disease, while the other had no medical history of note and was a life-long non-smoker. None of those with positive titres was on immunosuppressive therapy.

6. DISCUSSION

6.1 Study population

The participation rate in this study was high (88,4%). This may have been influenced by the fact that the study was conducted in old age homes. Residents of an old age home could be considered to represent a captive population and may be reluctant to be seen to be different from their fellow residents by refusing to participate. This may have resulted in a form of selection bias.

No data is available on those who refused consent or on those from whom a suitable blood specimen could not be obtained. In order to assess non-response bias a questionnaire on each of these should have been completed providing demographic details, as well as information as to health status, including mental and psychiatric status. It would also have been of value to determine why they did not wish to participate. If they had been found to differ from the participants in a consistent or systematic way, this too might have allowed analysis for study sample bias (non-participant bias). It is possible that subjects with dementia might be more likely to refuse to participate, and, as many of the residents of these homes suffered from dementia, this may have been one of the reasons for non-participation in this study. Any subject with acute confusion, eg due to an illness such as *Legionella* pneumonia, might be similarly uncooperative. Lack of suitable data does not permit verification of this, but it could mean that subjects who were ill might have been excluded contributing to falsely low prevalence data.

The fact that participants in the present study were all residents of old age homes and not community dwelling elderly may be of particular relevance. Mycoplasma is spread from person to person by infected droplets, but is not highly contagious. Close contact is essential, and the prevalence in closed communities is known to be increased (Luby, 1991). An old age home could be considered to constitute a closed community especially in the case of the more infirm residents who are confined to frail care units and thus live in close proximity to one another. This may, in fact, lead to an increased exposure to mycoplasma in old age homes with a consequent greater prevalence of mycoplasmal antibodies than in the general community dwelling elderly population. It is also possible that longer duration of residence within the home may predispose to infection.

By contrast, *Legionella* is not spread from person to person, but by inhalation of infected water which has been aerosolised (Edelstein & Meyer, 1984). The fact that the prevalence of *Legionella* seropositivity in these homes was so low and that there was no clustering of positive sera from a single home suggests that a point source of infection within the home itself was highly unlikely, and that the infection may have been acquired elsewhere.

Although the stated objective was to assess antibody prevalence in the elderly in old age homes in Cape Town, only those resident in the 4 participating old age homes were included. Ideally we would have liked to include elderly black persons in the study sample, but, for the reasons given earlier, this was not possible. As a result, no black elderly were included, so the sample is not truly representative of the elderly in Cape Town, nor indeed of the old age home population, leading to possible sample bias. The generalisability of the results obtained to the elderly population of Cape Town as a whole are thus subject to question. For socio-economic

reasons, black families tend to live in more cramped conditions and the elderly have greater exposure to children. This may enhance the likelihood of droplet spread, and may predispose to mycoplasma infection in black elderly. In addition, those who were more ill (eg those who had *Legionella* pneumonia), might have died, and would thus have been excluded from any serological survey. Data on those who died are not included. It is thus conceivable that there is an underestimation of the prevalence of both mycoplasma and *Legionella* seropositivity in this study.

6.2 Sample size

The sample was not random nor a true cluster sample, and sample size was not determined in advance. The sample was merely drawn from those in the 4 old age homes who were over 60, willing to participate, and from whom blood could be obtained without too much difficulty. The sample could thus be described as a "convenience" sample.

A calculation was done in order to determine what an appropriate size would have been had the sample been chosen at random, and assuming an expected frequency of seropositivity of 2,5%.

There are no comprehensive data available as to the numbers of people resident in old age homes in Cape Town. Data from the Population Census of 1991 were used to determine the number of elderly in Cape Town (Table 10). The only figures available were for females aged 60 and over and for males aged 65 and over. This means that males aged 60 to 65 are not included in the calculation, resulting in an underestimation of the population under

investigation. A total of 142,322 was obtained of whom 96,738 were female and 45,584 were male. A figure of 150,000 was used for the population size in the calculation.

The Statcalc function of the Epi Info programme was used to do the determination (Appendix II). Using a population size of 150,000 and assuming an expected frequency of 2,5%, a sample size of 657 would be needed for a confidence level of 99,9%. This is comparable with the 677 who actually participated in the study.

6.3 Consent

Each of the old age homes in which the study was conducted housed a significant number of residents who were mentally frail. As a result, it was decided that proxy consent provided by the matron or by a relative would suffice where written consent could not be obtained from the resident him/herself. The fact that the procedure by which the blood specimen was obtained was not an unduly invasive one meant that we did not feel obliged to contact a family member in each case where the resident was not competent to give consent. In no case was coercion used. However, it remains open to question as to whether the procedure used to obtain consent was adequate in all instances.

6.4 Methods

The accuracy and completeness of the medical details on the questionnaire depended to a large extent on what appeared in each resident's medical records. For most of the residents, medical attention was provided by the district surgeon attending the home or by the doctor at the nearest Day Hospital. However, a proportion were cared for by private medical practitioners, and, as a group, they tended to make scanty notes in the records held by the home. The information that we were able to extract may thus have been lacking in some details causing information bias. Private practitioners were not contacted to ensure that such deficiencies did not exist.

6.5 Seropositivity to *Mycoplasma pneumoniae*

In this study the antibody titre in a single specimen only was obtained, the purpose being to determine exposure to the organism and not to diagnose acute infection. The presence of IgM antibodies would normally suggest current or recent infection, although, as mentioned earlier, in older persons little or no IgM may be produced (Moule & Caul, 1987; Uldum et al., 1992). Only 9 subjects had detectable levels of IgM, and these were low with titres of 16 in 1 and 8 in the remaining 8, suggesting that none of these subjects had had an acute or recent infection. The low titres could be due to poor antibody production, to waning titres from previous infection, or may represent cross-reactivity.

There were 16 subjects with detectable IgG titres. In 15 the titre was 32 or greater in keeping with previous infection at some time in the past, while in 3 the titre was 64 and may represent

more recent infection. The fact that IgM titres in these 3 were low (8) or undetectable would tend to make current infection unlikely. The single IgG titre of 8 may be insignificant or may represent a waning titre from an infection in the more distant past.

The interpretation of antibody levels is made difficult not only by the cyclical nature of mycoplasmal infections, but also by the fact that antibody levels in patients who have had mycoplasmal pneumonia may remain elevated for as long as 3 years (Foy et al., 1983). In addition, because mycoplasmal infection may be asymptomatic, antibodies to mycoplasma may be detected in subjects who have no history of previous mycoplasmal infection. Several studies have assessed the prevalence of antimycoplasmal antibodies in healthy members of the population (Table 9). Results are difficult to compare because techniques for antibody detection vary, as do titres considered positive. However, positivity rates have tended to be low with low titres recorded, varying from <1% to 16% at a titre of 64 (Table 9). No study has specifically addressed this question in older members of the community, and only 0,4% in the current study had a titre of 64, most (2,4%) having a titre of only 8.

The only other South African study which determined seropositivity to mycoplasma was that of Ross and Harwin (1972) in which 287 blood donors aged 18 to 65 were screened. Using the metabolic inhibition technique they found titres of ≥64 in 0,7%. No indication is given as to what proportion of the sample was aged 60 and older. As these were blood donors, it might safely be assumed that those in this older age group formed a very small proportion of the study population. Selection bias in blood donors would have favoured subjects who had not recently had pyrexial illnesses, and would thus have tended to exclude subjects with recent acute symptomatic mycoplasmal infection.

6.6 Seropositivity to *Legionella pneumophila*

Of the few studies in the literature describing seropositivity rates to *Legionella*, none deals specifically with the elderly, although the mean age in the study among medical outpatients by Nichol et al. (1991) was 67 years (Table 10). The prevalence rate found in our study (mean age 78 years) is thus difficult to compare with published reports, since the relative impact of the background population prevalence is as yet unknown.

All 9 sera in this study which were regarded as positive had titres of 128 or above, while in only 3 the titre was 256 or greater. No history was taken specifically to elicit symptoms which could be attributable to recent *Legionella* infection. In any case, most cases of *Legionella* infection are subclinical or asymptomatic. For that reason, in this study all sera with titres of 128 or above were regarded as being positive and suggestive of acute or recent infection.

The epidemiological implications of the seropositivity rates found in this study are open to question. Whilst reports indicate that *Legionella* antibody titres remain elevated for years after the acute infection, it is not known whether age has any influence on the antibody response or the duration of antibody positivity (Tsai et al., 1979; Nguyen & Yu, 1991; Kirby et al., 1980). In this study it is not possible to tell if any of the positive antibody titres was due to a recent infection, as this information was not specifically sought. However, one of the subjects was receiving treatment for a lower respiratory tract infection and had a titre of 256. This may represent a current infection with *Legionella*. The 2 subjects with the highest titre (512) had no history to suggest an acute infection in the recent past. It must be noted, however, that demented residents may not complain of feeling unwell, and that manifestations of respiratory

tract infection might go unnoticed by the staff. It has been shown that in some instances positive *Legionella* titres may be due to cross-reacting antibodies due to Gram-negative bacilli, mycoplasma, or chlamydia (Grady & Gilfillan, 1979; Ormsbee et al., 1978; Nguyen & Yu, 1991). Since these sera were tested for *Mycoplasma pneumoniae*, and none had positive titres, this would seem an unlikely explanation.

Although male sex has been shown to be a risk factor for *Legionella*, the proportion of males with positive titres (2/174 = 1,14%) is, in fact, smaller than in the females in the study group (7/503 = 1,39%). Those with positive titres do not appear to have more chronic illnesses than elderly people in general or than the study population as a whole. This would tend to support the contention that while these characteristics place people at greater risk for developing *Legionella* pneumonia, subclinical infection may be more closely related to the likelihood of environmental exposure to the organism.

There are 2 South African studies which have assessed seropositivity to *Legionella* in healthy subjects (Table 10). The first is that of Ratshikhopha et al. (1990) in which 456 blood donors (mean age 32,1 years) were screened. The proportion with significant titres was higher than in our study with 28,3% having IgG titres ≥64 and 12,5% IgM titres ≥64.

A similar study was performed among blood donors in Cape Town by de Goveia (1989) and submitted as part of an MMed thesis. Of the 200 donors screened (ages<20 to >60, 6 being ≥60) 8 (4%) had titres ≥64. Of these 2 (a third) were aged 60 or over.

Although both these studies used the indirect fluorescent antibody technique using heat killed antibody (the same technique as used in this study), the results cannot really be compared. It is not evident how many in the study by Ratshikhopha et al. (1990) were aged 60 or older, while in the study by de Goveia (1989) only 6 of the 200 fell into this age group. The fact that as many as a third of the elderly in the latter study had antibodies to *Legionella* may simply have been fortuitous, given the extremely small sample in that age group. Note that in the current study only titres ≥128 were sought.

6.7 The role of serology in healthy subjects

Determining the seropositivity rate to specific organisms among healthy (non-ill) members of the community gives an indication of previous exposure to the organism in the community (Nichol et al., 1991). It is interesting to note that this background prevalence rate represents the false positive rate for a single antibody titre if it is to be used to establish a diagnosis of acute infection. The higher the background titre (false positive rate) in the specific population being tested, the lower will be the specificity and sensitivity of that test in the particular population.

The indirect fluorescent antibody test was designed to diagnose acute infection, and the sensitivity and specificity of the test relate to its ability to do just that. The Centre for Disease Control definition of a probable case of acute *Legionella* infection requires that there be a compatible illness plus the demonstration of a single antibody titre to *Legionella pneumophila* ≥256. The sensitivity and specificity of a fourfold rise in antibody titre to *Legionella pneumophila* serogroup 1 have been estimated at 80% and 95% respectively (Wilkinson,

1982; Wilkinson et al., 1983). However, the specificity of a single elevated titre is directly related to the background positivity rate for the population from which the patient comes, which, as indicated above, represents the false positive rate.

In this study the false positive rate for a single titre ≥128 would be 1,33%, and so the specificity of a single titre ≥128 in diagnosing acute infection would be 98,7% (specificity = 1 - false positive rate) (Sackett et al., 1985). Hence, in our population a single titre of only 128 may be regarded as diagnostic. All 9 with positive titres in this study had titres ≥128, but only one appeared to have acute disease (the subject whose titre was 256). It might under these circumstances be presumed that they all had had recent *Legionella* infection, albeit asymptomatic.

The Zeus indirect fluorescent antibody test (Zeus Scientific Inc.) for IgM antibodies to *Mycoplasma pneumoniae* is 77,3% sensitive and 97,6% specific, while the test for IgG is 94,4% specific (Zeus Scientific Inc.). The false positive rate for a single IgG titre ≥64 in our population would be 1,33% (3/677), so the specificity of a single titre ≥64 would be 98,7% (100 - 1,33). Titres of IgM are very low, but from this study a single titre ≥16 (presuming no cross-reactivity) would be 99,8% (100 - 0,15). Hence, it appears that this test is highly specific, but not 100% sensitive.

7. CONCLUSIONS AND RECOMMENDATIONS

This is the first study of its type in South Africa which has specifically sought to determine the prevalence of seropositivity to *Legionella* and mycoplasma in elderly persons. It is recognised that this study has several limitations which relate mainly to the choice of sample, and the fact that information regarding non-participants was not specifically sought. These factors may have introduced bias. The major drawback is that the results obtained, while being applicable to the population in which the study was conducted, may not be generalisable to elderly South Africans as a whole. However, for the reasons put forward in the Discussion, it is argued that the prevalence of *Legionella* seropositivity in this study is likely to be an under-estimate of the status of the general South African elderly population, while the direction of bias of the seropositivity rate for mycoplasma remains unknown.

This study has shown that, amongst the elderly in the old age homes studied, the prevalence of antibodies to *Legionella* and mycoplasma is low. This suggests that exposure to infection with these 2 agents is not common, and that they do not constitute significant causes of community acquired pneumonia in this population. This mitigates against the need for empiric antibiotic therapy in most elderly patients presenting with community acquired pneumonia which includes antimicrobial agents active against *Legionella* or mycoplasma, and is in keeping with the current recommendation of the South African Pulmonology Society (1996) that first-line treatment of community acquired pneumonia should be a parenteral second generation cephalosporin or co-amoxiclav. However, there are exceptions where infection with one of these agents may seem likely, and this may prompt the addition of erythromycin, tetracycline,

or another macrolide while seeking serological confirmation of the diagnosis. Features such as minimal sputum production, the absence of a predominant organism on Gram stain, prominent constitutional symptoms such as headache or fever, or the presence of extrapulmonary manifestations such as diarrhoea, vomiting, arthralgia or myalgia might be suggestive, as would failure to respond to treatment with penicillin or a cephalosporin within 48 to 72 hours. It must, however, be remembered that elderly patients with bacterial pneumonia may have an atypical presentation, especially if the pneumonia is severe. In addition, in our area, tuberculosis may present as an acute pneumonia, particularly in old age homes, and may need to be excluded.

As has been indicated earlier, the false positive rate of the indirect fluorescent antibody test for these 2 organisms in this population is low, and as a result the specificity of these tests is high. This may be of value in making a diagnosis of acute infection with either agent in an elderly patient with a compatible clinical picture, in that a positive antibody titre (even if relatively low) might be regarded as being highly specific and may permit a presumptive diagnosis of acute infection on a single specimen, although a fourfold rise on paired acute and convalescent sera would be the ideal.

Several areas remain to be elucidated as regards infection with these 2 organisms in the elderly. While this study was conducted in old age homes, there is still no clear idea as to the level of exposure to *Legionella* and mycoplasma in the general community dwelling elderly population. It is recommended that a community-based survey be undertaken to assess this.

While certain aspects of the immunology of these agents is known, much remains to be determined, especially with regard to older persons. In particular, studies should be directed at investigating the immunoreactivity of the elderly to these 2 agents, as well as determining the pattern of antibody response and decay in older persons, as this will assist in interpreting the results of serology conducted in those presenting with acute disease.

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TABLE 1: AETIOLOGY OF COMMUNITY ACQUIRED PNEUMONIA IN ADULTS

Author (mean age of subjects)	Country Year	No. of Cases	Aetiologic Agent (%) First	Second	Third	No Pathogen Identified (%)	Mortality (%)
Blanquer (58)	Valencia Spain 1991	510	Pneumococcus (45)	*Legionella* (14)	Mycoplasma (4)	45	6
British Thoracic Society (48)	Multicentre UK 1987	453	Pneumococcus (34)	Mycoplasma (18)	Influenza A (7)	33	6
Fang (62)	Pittsburgh USA 1990	359	Pneumococcus (15)	*H.influenzae* (11)	*Legionella* (7)	41	14
Fine (57)	Boston USA 1990		Pneumococcus (13)	*H.influenzae* (8)	Staphylococcus (5)	65	13
Karalus (56)	Waikato New Zealand 1991	92	Pneumococcus (33)	Mycoplasma (18)	Influenza A (8)	18	7
Lim (60)	Adelaide Australia 1989	106	Pneumococcus (42)	*H.influenzae* (9)	Entero-bacteriaceae (8)	33	10
MacFarlane (51)	Nottingham UK 1982	127	Pneumococcus (76)	*Legionella* (15)	Chlamydia (5)	3	15
Marrie (46)	Nova Scotia Canada 1985	57	Aspiration (23)	*H.influenzae* (14)	Pneumococcus (12)	30	10
Pachon (57)	Seville Spain 1990	67	Pneumococcus (18)	*Legionella* (10)	-	52	21
Rello (45)	Barcelona Spain 1993	58	Pneumococcus (37)	*Legionella* (23)	Gram-negative bacilli (11)	40	22
White (54)	Bristol UK 1981	103	Mycoplasma (14)	Pneumococcus (11)	Influenza A (10)	52	8
Woodhead (59)	Nottingham UK 1987	236	Pneumococcus (36)	*H.Influenzae* (10)	Influenza A (6)	45	3

TABLE 2: AETIOLOGY OF COMMUNITY ACQUIRED PNEUMONIA IN ELDERLY

Author (mean age of subjects)	Country Year	No. of Cases	Aetiologic Agent (%) First	Second	Third	No Pathogen Identified (%)	Mortality (%)
Carr (77)	Dublin Ireland 1991	127	Pneumococcus (37)	*H.influenzae* (18)	*B.catarrhalis* (10)	39	11
Ebright (≥65)	Milwaukee USA 1980	33	Gram-negative bacilli (21)	Pneumococcus (18)	*S.aureus* (6)	54	24
Garb (76)	Springfield Mass USA 1978	35	Gram-negative bacilli (57)	Pneumococcus (43)	*H.influenzae* (20)	-	20
Harper (78)	Portland Oregon USA 1989	48	*H.influenzae* (33)	Pneumococcus (23)	Mixed (16)	-	12
Marrie (77)	Novo Scotia Canada 1985	81	Aspiration (9)	Cytomegalo-virus (9)	Pneumococcus (7)	54	30
Venkatesan (79)	Nottingham UK 1990	73	Pneumococcus (30)	*H.influenzae* (7)	Influenza B (7)	57	33
Verghese (-)	Tennessee USA 1983	32	Gram-negative bacilli (47)	Pneumococcus (34)	*H.influenzae* (28)	-	33

TABLE 3: PROPORTION OF CASES OF ADULT COMMUNITY ACQUIRED PNEUMONIA CAUSED BY MYCOPLASMA OR *LEGIONELLA*

AUTHOR YEAR	COUNTRY	No. of Cases	MYCOPLASMA %	*LEGIONELLA* %
Blanquer 1991	Spain	510	14	4
British Thoracic Society 1987	UK	453	18	2
Fang 1990	USA	359	2	7
Karalus 1991	New Zealand	92	18	4
Lim 1989	Australia	106	8	3
Maartens 1994	RSA	92	1	9
MacFarlane 1982	UK	127	2	15
Marrie 1985	Canada	57	2	2
Pachon 1990	Spain	67	0	10
Potgieter 1992	RSA	95	1	5
Prout 1983	RSA	81	10	0
White 1981	UK	103	14	1

TABLE 4: AGE SPECTRUM OF CASES OF *MYCOPLASMA PNEUMONIAE* PNEUMONIA

AUTHOR (AGE RANGE)	COUNTRY YEAR	No. of Cases	Percentage (No.)	Age (Yrs)
Ali (4-82y)	Norwich UK 1986	47	40% (19) 74% (35) 21% (10)	<20 <40 >60
Dular (2-59y)	Ottawa Canada 1987	51	65% (33) 35% (19)	<20 >20
Mansel (3m-77y)	Minnesota USA 1989	148	91% (134) 9% (14)	<40 >40
Marrie -	Nova Scotia Canada 1993	64	91% (58) 9% (6)	<65 65+

TABLE 5: MORTALITY RATES DUE TO MYCOPLASMA OR *LEGIONELLA*

AUTHOR (YEAR)	COUNTRY	MYCOPLASMA % MORTALITY	*LEGIONELLA* % MORTALITY
Ali (1986)	UK	3	-
Blanquer (1991)	Spain	0	10
British Thoracic Soc (1987)	UK	5	0
Carr (1991)	Ireland	0	-
England (1981)	USA	-	19
Fang (1990)	USA	0	17
Karalus (1991)	New Zealand	0	0
Lim (1989)	Australia	0	0
MacFarlane (1982)	UK	0	0
Mansel (1989)	USA	0	-
Marrie (1985)	Canada	0	0
Pachon (1990)	Spain	-	0
Potgieter (1992)	RSA	0	0
Prout (1983)	RSA	0	-
Rello (1993)	Spain	-	25
White (1981)	UK	3	67
Woodhead (1987)	UK	0	16

TABLE 6: PARTICIPANTS WITH ANTIBODIES TO MYCOPLASMA

STUDY NUMBER	IgG TITRE (n=16)	IgM TITRE (N=9)
391	8	
22	32	
47	32	
131	32	
268	32	8
377	32	
393	32	
397	32	8
405	32	8
431	32	8
536	32	8
651	32	8
660	32	8
198	64	
520	64	8
521	64	
661		16

TABLE 7: PARTICIPANTS WITH ANTIBODIES TO *LEGIONELLA*

STUDY NUMBER	ANTIBODY TITRE (n=9)
65	128
68	128
115	128
479	128
503	128
546	128
76	256
256	512
580	512

TABLE 8: NUMBERS OF ELDERLY IN CAPE TOWN (DATA FROM 1991 CENSUS PROVIDED BY DEVELOPMENT BANK OF SOUTH AFRICA)

MAGISTERIAL DISTRICT	FEMALES 60+	MALES 65+	TOTAL
Bellville	14086	6606	
Goodwood	13406	5648	
Cape Town	18350	8557	
Kuils River	3002	1334	
Simonstown	5035	2754	
Wynberg	42859	20685	
TOTALS	96738	45584	142322

TABLE 9: MYCOPLASMA ANTIBODIES IN "HEALTHY" SUBJECTS

AUTHOR (YEAR)	COUNTRY	STUDY SIZE	SUBJECTS (AGE)	TECHNIQUE	POSITIVITY RATE %	TITRE (%)		
Gnarpe (1992)	Sweden	422	Blood donors (16-76)	Latex agglutination	29	≥40 (27) ≥160 (2)		
Lind (1976)	Denmark	515	WR specimens (0-20) Histocompat spec (4-16) Blood donors Recruits	Complement fixation	3	Low		
Pearce (1986)	New Zealand	1461	Blood donors (16-65)	Complement fixation	16	≥64		
Ross (1972)	South Africa	287	Blood donors (18-65)	Metabolic inhibition	17	≥2 (16) ≥64 (1)		
							IgG	IgM
Current Study	South Africa	677	OAH residents (60-98)	Indirect fluorescent antibody	2,5	≥8 ≥32 ≥64	(2,4) (2,2) (0,4)	(1,3)

TABLE 10: *LEGIONELLA* ANTIBODIES IN SERA FROM "HEALTHY" DONORS

AUTHOR (YEAR)	COUNTRY	STUDY SIZE	SUBJECTS (AGE)	TECHNIQUE	POSITIVITY RATE %	TITRE (%)
Bettelheim (1982)	New Zealand	500	National Serum Bank (<20->50)	Indirect fluorescent antibody	31	≥32
De Goveia (1989)	RSA	200	Blood donors (<20->60)	Indirect fluorescent antibody (heat killed)	4	≥64
Edson (1979)	USA	1200	VDRL specimens (15->60)	Haemagglutination	19	≥32
Macrae (1979)	UK	2023	Antenatal Clinic Housing Dept Miners Industry Pest Control	Indirect fluorescent antibody	1	≥32
Nichol (1991)	USA	396	Medical OPD (mean 67)	Indirect fluorescent antibody (formalin killed)	71	≥64 (71) ≥128 (36) ≥256 (18)
Ratshikhopha (1990)	RSA	456	Blood donors (mean 32)	Indirect fluorescent antibody (heat killed)	28	IgG IgM ≥8 (74) (46) ≥64 (28) (12) ≥128 (16) (5)
Current Study	RSA	677	OAH residents (60-98)	Indirect fluorescent antibody (heat killed)	1,3	≥128

APPENDIX I

NO 1 ☐☐☐

HOME: A = 1 Z = 2 L = 3 E = 4 2 ☐

BASELINE ENTRY

DATE OF ENTRY: D/M/Y 3 ☐☐☐☐☐☐

SURNAME:

FIRST NAMES:

DATE OF BIRTH: D/M/Y 4 ☐☐☐☐☐☐

GENDER: M = 1 F = 2 5 ☐

NO OF PERSONS IN BEDROOM: 6 ☐

DURATION IN RESIDENCE (YEARS): 7 ☐

CURRENTLY IN FRAIL-CARE: Y = 1 N = 2 8 ☐

HEALTH STATUS

CVS:

IHD Y = 1 N = 2	9 ☐
HYPERTENSION	10 ☐
CCF	11 ☐
OTHER: SPECIFY	12 ☐

RESP:

CHRONIC BRONCHITIS	13 ☐
EXERTIONAL DYSPNOEA	14 ☐
TREATMENT FOR ASTHMA	15 ☐
SMOKING: CURRENT = 1 PREVIOUS = 2 NEVER = 3	16 ☐
IF CURRENT: NO PER DAY	17 ☐☐
IF PREVIOUS: YEARS SINCE STOPPING	18 ☐☐
TUBERCULOSIS:	
CURRENT = 1 PREVIOUS = 2 NEVER = 3	19 ☐
OTHER: Y = 1 N = 2	20 ☐

DIABETES: Y = 1 N = 2 21 ☐

OTHER PROBLEMS: Y = 1 N = 2 22 ☐

SPECIFY:

FUNCTIONAL STATUS

MOBILITY: 23☐
MOVES ABOUT WITHOUT ASSISTANCE = 0
ASSISTANCE AND SUPERVISION WITH MOBILITY
(ALSO WALKING AIDS AND WHEELCHAIRS) = 2
BEDRIDDEN OR TOTALLY IMMOBILE = 4

MAKING OF BED: 24☐
CAN DO IT HIMSELF = 0
NEEDS ASSISTANCE = 1
MUST BE DONE FOR HIM = 2

WASHING OF HANDS AND FACE: 25☐
DOES IT HIMSELF = 0
NEEDS ASSISTANCE OR SUPERVISION = 1
HAS TO BE WASHED = 2

BATHING: 26☐
UNAIDED = 0
NEEDS ASSISTANCE = 1
HAS TO BE WASHED = 2

SHAVING & COMBING OF HAIR: 27☐
DOES IT HIMSELF = 0
NEEDS ASSISTANCE = 1
HAS TO BE DONE FOR HIM = 2

FEEDING: 28☐
ENJOYS MEALS UNAIDED IN DININGROOM = 0
MEALS MUST BE SERVED IN BEDROOM = 2
MUST BE ASSISTED OR SPOON-FED = 4

DRESSING: 29☐
DOES IT HIMSELF = 0
NEEDS ASSISTANCE OR SUPERVISION = 1
MUST BE DRESSED AND UNDRESSED = 2

EYESIGHT: 30☐
GOOD OR FAIR = 0
BAD = 1
BLIND OR ALMOST BLIND = 2

HEARING: 31☐
GOOD OR FAIR = 0
BAD = 1
DEAF OR ALMOST DEAF = 2

MEMORY: 32☐
NORMAL = 0
FORGETFUL = 1
VERY BAD = 2

COMPREHENSION: 33
- NORMAL = 0
- BAD = 1
- MINIMAL = 2

GENERAL MENTAL CONDITION: 34
- NORMAL = 0
- AT TIMES DISTURBED OR CONFUSED = 2
- DISTURBED, CONFUSED OR PSYCHOTIC = 4

INCLINATION TO FITS: 35
- NONE = 0
- LIGHT FITS, DIZZINESS OR EPILEPSY = 1
- SERIOUS FITS = 2

INCONTINENCY: 36
- NONE = 0
- PARTLY INCONTINENT = 2
- INCONTINENT = 4

MEDICATIONS: Y = 1 N = 2

STEROIDS	37
BRONCHODILATORS	38
ANTIANGINAL THERAPY	39
ANTIFAILURE THERAPY	40
ANTIHYPERTENSIVE THERAPY	41
PSYCHOTROPIC AGENTS	42
ANTICONVULSANTS	43
NON-STEROIDAL ANTI-INFLAMMATORY AGENTS	44
ANTACIDS, THERAPY FOR PEPTIC ULCERATION	45
ANTIBIOTICS, ANTI-TB THERAPY	46
ANTIDIABETIC AGENTS	47
ANTIPARKINSONIAN THERAPY	48
ANALGESICS	49
VITAMINS & HAEMATINICS	50
ANTICOAGULANTS, ANTIPLATELET AGENTS	51
OTHER	52

FLU' VACCINATION STATUS:

1990	Y = 1 N = 2		53
	DATE D/M/Y		54
1991	Y = 1 N = 2		55
	DATE D/M/Y		56

BLOOD FOR SEROLOGY Y = 1 N = 2

LEGIONELLA:	POS = 1	NEG = 2	57
MYCOPLASMA:	POS = 1	NEG = 2	58
CHLAMYDIA:	POS = 1	NEG = 2	59
			60

APPENDIX II

Population Survey or Descriptive Study Using Random (Not Cluster) Sampling

Population Size	150,000
Expected Frequency	2.50 %
Worst Acceptable	0.05 %

Confidence Level	Sample Size
80%	100
90%	165
95%	234
99%	403
99.9%	657
99.99%	917

Formula: Sample Size = n/(1-(n/population))
n=Z*Z(P(1-P))/(D*D)

Reference: Kish & Leslie, Survey Sampling, John Wiley & Sons, NY, 1965.